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SUSCEPTIBILITY TO ACUTE MOUNTAIN SICKNESS: RELATIONSHIP TO PRE-ASCENT RESTING VENTILATION

U.S. ARMY RESEARCH INSTITUTE
OF
ENVIRONMENTAL MEDICINE

Natick, Massachusetts
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The objective of this study was to determine if the magnitude of the sea level pre-ascent resting ventilation and hypoxic ventilatory depression (HVD) are selective in identifying subjects who are susceptible to AMS. We hypothesized that individuals with lower effective alveolar ventilation, i.e., high resting end-tidal carbon dioxide partial pressure (PETCO2), and high HVD will be more likely to develop AMS during subsequent exposure to 4300 m. Twenty volunteers spent 24 h in a hypobaric chamber at sea level undergoing baseline measurements. During this baseline period, the subjects completed sea level resting ventilation and HVD procedures. The next morning, the chamber was decompressed to simulated altitude (PB 430 or 446 mmHg) for approximately 32 h. Resting ventilation was measured after about 4 hours exposure to high altitude and AMS assessed using the Environmental Symptoms Questionnaire at 8-hour intervals throughout the altitude exposure. At sea level, all subjects had normal levels of ventilation and exhibited no evidence of hypoxemia. There was a wide distribution in the resting PETCO2, and HVD. At about 4 hours exposure to high altitude, both SaO2 and PETCO2 were lower ($p < 0.002$) compared to sea level. The distribution of PETCO2 and particularly SaO2 widened at high altitude. The sea-level normoxic PETCO2 was positively correlated to the high altitude PETCO2. Sixty percent of the volunteers developed AMS (AMS+) at some point during their altitude exposure. The resting SaO2 in the AMS+ group tended ($p = 0.193$) to be lower than the 40% not developing AMS (AMS-). The sea level HVD was significantly higher in the AMS+ group compared to the AMS- group; but there was a wide overlap in its distribution between the groups. None of the other sea level ventilatory measurements were meaningfully different between the AMS+ and AMS- groups. We conclude that sea level pre-ascent measures of ventilation during normoxic or sustained isocapnic hypoxia were minimally effective in identifying AMS-susceptible versus non-susceptible subjects.

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BACKGROUND

Mountain environments are likely areas of military confrontation. Mountain ranges typically form the borders of nations, and numerous regions of geopolitical interest to the U.S. such as the Balkans, South America, the Middle East, and Asia contain extensive areas of moderate (>1500 m) to high (>2400 m) altitudes. Rapid force projection to such altitudes presents challenges in sustaining optimal military performance due to the hypoxia associated with altitude exposure and its deleterious affect on mission-related work activities. Acute Mountain Sickness (AMS), caused by hypobaric hypoxia, will negatively impact military operations. Current interventions to prevent AMS include slow or staged ascent and select pharmaceuticals. However, each currently available procedure or medication for prophylaxis or treatment of AMS can constrain or degrade mission effectiveness independent of AMS. Susceptibility to AMS is not uniform. Thus, identifying individuals most susceptible to AMS may help limit the need for widespread use of prophylactic medication by targeting only those AMS-susceptible individuals. Currently, there are no known physiological markers of AMS susceptibility other than prior high altitude exposure and history or absence of high altitude illness. Thus, there is a need to evaluate promising physiological indices of AMS susceptibility. This study was funded under U.S. Army Medical Research and Materiel Command Scientific and Technical Objective J.

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EXECUTIVE SUMMARY

Acute Mountain Sickness (AMS) is a multi-system disorder that is principally characterized by headache, anorexia, nausea, vomiting, insomnia, lassitude, and malaise. The syndrome is common in unacclimatized low altitude residents who rapidly ascend to terrestrial elevations exceeding 2,500 m. The symptoms usually appear within 24 h of exposure and normally resolve after several days. Acute Mountain Sickness is usually self-limited, but may progress into high altitude cerebral edema (HACE) or high altitude pulmonary edema (HAPE), both of which are life-threatening.

The balance of data suggests a relatively greater hypoxemia in AMS-susceptible subjects compared to non-susceptible subjects at high altitude. This greater hypoxemia may result from a low hypoxic ventilatory response (HVR), high hypoxic ventilatory depression (HVD) and/or impaired pulmonary gas exchange.

The objective of this study was to determine if the magnitude of the sea level pre-ascent resting ventilation and HVD are selective in identifying subjects who are susceptible to AMS. We hypothesized that individuals with lower effective alveolar ventilation, i.e., high resting end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$), and high HVD will be more likely to develop AMS during subsequent exposure to 4300 m.

This report documents the relationship between resting ventilation and AMS in two related studies of AMS. One study involved 8 male volunteers exposed to a simulated altitude of 4572 m (P_B 430 mmHg) in a hypobaric chamber for approximately 32 h. The second study involved 12 women volunteers exposed to a simulated altitude of 4300 m (P_B 446 mmHg) in the same hypobaric chamber for approximately 34 h. Other than the different altitudes, the methods, procedures and test schedules utilized in each study were nearly identical. For each study, volunteers first spent 24 h in the hypobaric chamber at sea level undergoing baseline measurements. During this baseline period, the subjects completed sea level resting ventilation, HVR and HVD procedures. The next morning, the chamber was decompressed to altitude. Resting ventilation was measured after about 4 hours exposure to high altitude and AMS assessed using the Environmental Symptoms Questionnaire at 8-hour intervals throughout the altitude exposure.

At sea level, all subjects had normal levels of ventilation and exhibited no evidence of hypoxemia. There was a wide distribution in the resting $P_{ET}CO_2$, HVR and HVD. At sea level, there were no significant correlations between normoxic $P_{ET}CO_2$, normoxic $\dot{V}_E$, HVR or HVD. At about 4 hours exposure to high altitude, both SaO_2 and $P_{ET}CO_2$ were lower ($p<0.002$) compared to sea level. The distribution of $P_{ET}CO_2$ and particularly SaO_2 widened at high altitude. The sea-level normoxic $P_{ET}CO_2$ was positively correlated to the high altitude $P_{ET}CO_2$.

Sixty percent of the volunteers developed AMS (*AMS+*) at some point during their altitude exposure. The resting SaO_2 in the *AMS+* group tended ($p = 0.193$) to be lower than the 40% not developing AMS (*AMS-*). The sea level HVD was significantly higher in the *AMS+* group compared to the *AMS-* group; but there was a wide overlap in its distribution between the groups. None of the other sea level ventilatory measurements were meaningfully different between the *AMS+* and *AMS-* groups.

We conclude that sea level pre-ascent measures of ventilation during normoxic or sustained isocapnic hypoxia were minimally effective in identifying AMS-susceptible versus non-susceptible subjects. However, sea-level normoxic resting $P_{ET}CO_2$ was significantly related to the magnitude of effective ventilation at altitude, and may be useful in identifying individuals in need of slower or staged ascent profiles to induce acclimatization.

INTRODUCTION

Acute Mountain Sickness (AMS) is a syndrome that is characterized by headache, anorexia, nausea, vomiting, insomnia, lassitude, and malaise. The syndrome has great individual variation in susceptibility; however, the hypoxia-induced symptoms are most common in unacclimatized low altitude residents who rapidly ascend to terrestrial elevations exceeding 2,500 m (18). The symptoms of AMS commonly appear within 4 to 24 h of exposure, and usually resolve after several days as acclimatization to hypoxia is achieved. Acute Mountain Sickness is usually self-limited, but may progress into high altitude cerebral edema (HACE) or high altitude pulmonary edema (HAPE), both of which are potentially life-threatening.

There is evidence that AMS-susceptible subjects have a relatively greater degree of hypoxemia compared to well subjects at high altitude. Many studies have reported that compared to well subjects, subjects who will develop and who have developed AMS have either a lower alveolar ventilation, alveolar oxygen partial pressure (P_AO_2) or arterial oxygen saturation (SaO_2), or higher alveolar carbon dioxide partial pressure (P_ACO_2) (1,3,8,12,15,20,27). Although two recent studies (9,21) did not find significant differences in ventilation or SaO_2 between sick and well subjects at high altitude, the balance of data suggests a relatively greater hypoxemia in AMS-susceptible subjects compared to non-susceptible subjects at high altitude. This greater hypoxemia may result from a low hypoxic ventilatory response (HVR), high hypoxic ventilatory depression (HVD) and/or impaired pulmonary gas exchange.

The ventilatory response to sustained hypoxia is characterized by three phases (6,30). Phase I occurs within the first few minutes of hypoxic challenge, and is identified by an increase in ventilation due to stimulation of the peripheral chemoreceptors (i.e., HVR). However, this period of elevated ventilation is brief and followed by a decline in ventilation that may approach levels 25-50% of the peak response within 30 minutes (6,30). This hypoxic ventilatory depression (HVD) characterizes phase II and is present even during isocapnia (i.e., constant peripheral chemoreceptor stimulation). Therefore, it is believed to be of central origin (6,22,28,31). Finally, with prolonged (hours to days) exposure, ventilation progressively increases. This latter ventilatory response (phase III) is considered part of the altitude

acclimatization process (2,5,29). During the first hours following rapid ascent to high altitude, when AMS is developing, alveolar ventilation is most likely determined by a balance between HVR and HVD (11).

The magnitude of an individual's ventilatory response to acute and chronic poikilocapnic hypoxia (i.e., high altitude) is positively related to their sea level resting end-tidal ($P_{ET}CO_2$) (17,19). These two studies found a moderate degree of correlation (range 0.46 – 0.66) between their subjects' sea level and high altitude resting $P_{ET}CO_2$ during the first 48 h at 4300 m elevation. These data suggest that sea level resting $P_{ET}CO_2$ may identify subjects who will likely have low alveolar ventilation upon ascent to high altitude and thus be at greater risk for developing AMS.

Several studies have examined whether a low baseline HVR may be predisposing to AMS. In these studies, each subject's isocapnic HVR at low altitude was measured and subsequently compared to their AMS-susceptibility determined during a sojourn to high altitude (9,10,14). In two of the three studies (10,14), no correlation was found between baseline HVR and AMS-susceptibility in the 62 participating subjects. In the third study (9), the cumulative AMS severity scores of 12 subjects were inversely correlated with their baseline HVRs. Given that all three of these studies were mountaineering expeditions, a strong relationship between baseline HVR and AMS-susceptibility may have been obscured by other factors which influence AMS development such as rate of ascent, work/rest cycles, work rates, food and beverage consumption and exposure to temperature extremes.

A study by Moore et al. (15) looked at the relationship between ventilation at low and high altitudes and AMS in a hypobaric chamber. At their baseline altitude (1,600 m) AMS-susceptible subjects had a lower HVR than non-susceptible subjects. Moreover, compared to AMS non-susceptible subjects, AMS-susceptible subjects had a greater fall in their ventilation after 4.5 h exposure to 4,500 m altitude equivalent in a hypobaric chamber relative to their low altitude ventilation during acute poikilocapnic hypoxia. The authors proposed that the factors responsible for the symptoms of AMS or the symptoms themselves acted in conjunction with prolonged hypoxia to depress ventilation in symptomatic individuals. One known factor that could account for the fall in ventilation is HVD. However, at their baseline altitude (1600 m) both AMS

susceptible and non-susceptible subjects had similar decreases in ventilation (HVD) during 30 min of either isocapnic or poikilocapnic hypoxia. A possible reason for the lack of a difference between the AMS susceptible and non-susceptible subjects at baseline may have been that during their 30 min hypoxic exposure studies, the inspired oxygen concentration (FIO_2) was set at a different level for each subject. The authors adjusted the FIO_2 to achieve a similar level of SaO_2 (~81%) in each subject. Accordingly, subjects with greater HVD would have received a lower hypoxic stimulus (i.e., higher FIO_2) than subjects with a lower HVD. Thus, maintaining the SaO_2 constant should have minimized differences in the measured HVD and decreased the likelihood that a lower pre-ascent baseline altitude HVD would be detectable in the AMS-susceptible subjects.

OBJECTIVE

The objective of this study was to determine if the magnitude of the sea level pre-ascent resting ventilation, HVR and HVD are selective in identifying subjects who are susceptible to AMS. We hypothesized that individuals with lower effective alveolar ventilation, i.e., high resting $P_{ET}CO_2$ and high HVD will be more likely to develop AMS during subsequent exposure to 4300 m equivalent in a hypobaric chamber.

METHODS

SUBJECTS

Twenty volunteers (8 male, 12 female) with a mean (±SD) age and body weight of 23 ± 4 yrs and 66 ± 10 kg participated in this study. Each was a lifelong low altitude resident and had no exposure to altitudes greater than 1000 m for at least 6 months immediately preceding the study. All volunteers received medical examinations, and none were found to have any condition that would warrant exclusion from the study. All participated in regular physical training and were of average fitness. Each gave written and verbal acknowledgment of their informed consent and was made aware of their right to withdraw without prejudice at any time.

PROTOCOL

This study was conducted as a subpart of two studies of AMS. One study involved 8 male volunteers exposed to a simulated altitude of 4572 m (P_B 430 mmHg) in a hypobaric chamber for approximately 32 h. The second study involved 12 women volunteers

exposed to a simulated altitude of 4300 m (P_B 446 mmHg) in the same hypobaric chamber for approximately 34 h. All the women were studied in the follicular phase of their menstrual cycle determined by self-reporting and confirmed by ovarian hormone analysis. Other than the different altitudes, the methods, procedures and test schedules utilized in each study were nearly identical.

For each trial, volunteers first spent 24 h in the hypobaric chamber at sea level undergoing baseline measurements. During this baseline period, the subjects completed the sea level resting ventilation, HVR and HVD procedures. The next morning, the chamber was decompressed at the rate of 45 mmHg•min^{-1}. Food and fluid consumption was *ad libitum* throughout the study except for 2 h immediately preceding the ventilatory studies and one 8-h period in the early morning to facilitate body fluid compartment measurements, as dictated by a companion study. After ~32 h the chamber was recompressed to sea level, and the studies were concluded.

MEASUREMENTS

The Environmental Symptoms Questionnaire (ESQ) was used to assess AMS symptoms. The ESQ was administered at 0600 h and 2000 h during sea level testing and at 0600, 1200 h, and 2000 h at high altitude. The ESQ is a self-reported 67-question symptom inventory designed to quantify symptoms induced by altitude and other stressful environments and conditions (4). To document the presence of AMS, a weighted average of cerebral (AMS-C) and respiratory (AMS-R) symptoms were calculated from the ESQ scores (4). An AMS-C value of 0.7 or greater or an AMS-R value greater than 0.6 indicates the presence of AMS. The effectiveness of AMS-C scores in identifying individuals with AMS has been previously reported and validated (4).

All respiratory testing was performed in a comfortable, quiet laboratory setting. The subjects were studied after fasting at least 2 hours. During testing, subjects rested in a semi-supine posture while listening to music. Subjects breathed through a low resistance, non-rebreathing mouth/face mask (Hans Rudolph, Kansas City, MO) for at least 5 min before the start of data collection. Subjects were familiarized with the ventilatory tests a few days before the sea level studies.

For the sea level resting ventilation and steady-state, isocapnic-hypoxic ventilatory studies, the subjects breathed through a mask attached to a source of

inspired gas (room air or a hypoxic gas mixture: FIO_2 0.125, balance N_2). The following measurements were made: inspired flow with a heated pneumotachograph (Hewlett-Packard, Andover, MA), SaO_2 by pulse oximetry (SensorMedics Corp., Yorba Linda, CA), and inspired and expired carbon dioxide and oxygen concentrations by rapidly responding analyzers (LB-2, Beckman, Anaheim, CA and S3-A, Applied Electrochemistry, Inc., Sunnyvale, CA, respectively). All measured variables were continuously recorded on a PC-based data acquisition system (DATAQ Instruments, Inc., Akron, OH). Post-test, minute ventilation ($\dot{V}E$) was calculated from the integrated inspiratory flow, and $PETCO_2$ was identified from the PCO_2 data.

As shown in Fig. 1, during the 5-min baseline period at sea level, the subject breathed room air (normoxia [NOX]). From this data, the subject's $PETCO_2$ was identified. After baseline ventilation measures were obtained, the subject was switched, without warning, to the hypoxic gas source. Ventilatory responses to acute isocapnic hypoxia (AHX) were collected over the first 5-10 min and to chronic isocapnic hypoxia (CHX) over the last 5 min of the 30-min steady-state isocapnic hypoxic exposure. Isocapnia was maintained by addition of 100% CO_2 to the inspired gas. The HVR slope ($\Delta\dot{V}E \bullet \Delta SaO_2^{-1}$) was calculated from the initial $\dot{V}E$ rise in response to the AHX using least squares regression. The HVD was calculated: HVD ($l \bullet min^{-1}$) = $\dot{V}E_{AHX}$ - $\dot{V}E_{CHX}$. At high altitude, resting ventilation was measured after about 4 hours exposure.

STATISTICAL ANALYSIS

First, changes in ventilatory parameters from sea level to high altitude were compared using the Student T-test. Also, possible correlations between the sea level measurements and the high altitude measurements were evaluated using the Pearson Product-Moment Correlation method. Second, the subjects were then divided into two groups depending upon whether they developed or did not develop AMS (*AMS+*, or *AMS-*). Sea level and high altitude measurements of the *AMS+* and *AMS-* groups were compared using the Student T-test, or if the data deviated significantly from normality or failed to meet the qualifying assumptions of analysis of variance, the data were analyzed using the Mann-Whitney Rank Sum Test. Statistical significance was accepted at $p \leq 0.05$. Values are presented as mean ± standard deviation (SD).

RESULTS

At sea level, all subjects had normal levels of ventilation and exhibited no evidence of hypoxemia (Table 1). As expected, there was a wide distribution in the resting $P_{ET}CO_2$, HVR and HVD. At sea level, there were no significant correlations between normoxic $P_{ET}CO_2$ and the normoxic $\dot{V}_E$ or the HVR and HVD. After about 4 hours exposure to high altitude, both SaO_2 and $P_{ET}CO_2$ were lower ($p<0.002$) compared to sea level. The distribution of $P_{ET}CO_2$ and particularly SaO_2 widened at high altitude (Table 1). Subjects with high $P_{ET}CO_2$ at altitude had relatively lower SaO_2 ($r = -0.54$, $p=0.014$). The sea level normoxic $P_{ET}CO_2$ was positively correlated to the high altitude $P_{ET}CO_2$ ($r = 0.67$, $p = 0.001$), and negatively correlated to the high altitude $P_{ET}O_2$ ($r = -0.61$, $p = 0.005$) and SaO_2 ($r = -0.54$, $p=0.015$).

Twelve of the twenty volunteers (60%) developed AMS during the period of their high altitude exposure. Table 2 presents high altitude physiological measurements segregated by absence or presence of AMS. After about 4 hours exposure to high altitude, the resting SaO_2 in the *AMS+* group tended to be lower than in the *AMS-* group. Likewise, a weak negative correlation was observed between the subject's highest AMS-C score and their high altitude resting SaO_2 ($r = -0.39$, $p = 0.086$). Otherwise, there were no apparent ventilatory differences between the two groups at high altitude. When the sea level data were retrospectively analyzed based upon the presence or absence of AMS, the sea level HVD was significantly higher in the *AMS+* group verses the *AMS-* group (Table 3). However, there was a wide overlap in the distribution of the sea level HVD between the *AMS+* and *AMS-* groups (Figure 2). None of the other sea level ventilatory measurements distinguished between the *AMS+* and *AMS-* groups (Table 3).

Table 1. Resting ventilatory parameters at sea level and high altitude.

Variable	n	Mean	±S.D.	95% C.I. of Difference	p
Sea Level:					
$\dot{V}E$ ($l \cdot min^{-1}$)	20	9.5	2.2		
$P_{ET}CO_2$ (mmHg)	20	39.8	3.7		
$P_{ET}O_2$ (mmHg)	20	109.4	4.8		
SaO_2 (%)	20	97	1		
HVR ($\Delta\dot{V}E \cdot \Delta SpO_2^{-1}$)	20	0.42	0.26		
HVD ($l \cdot min^{-1}$)	20	1.75	1.70		
High Altitude:					
$\dot{V}E$ ($l \cdot min^{-1}$)	20	9.5	2.7	-1.5 to 1.6	0.989
$P_{ET}CO_2$ (mmHg)	20	35.7	3.9	1.6 to 6.5	0.002
$P_{ET}O_2$ (mmHg)	20	50.9	6.0	55.1 to 62.0	0.001
SaO_2 (%)	20	79	8	14 to 21	0.001*

*Mann-Whitney Rank Sum Test

Table 2. AMS symptom scores and resting ventilatory parameters at high altitude segregated by AMS susceptibility.

Variable	n	Mean	±S.D.	95% C.I. of Difference	p
AMS-:					
ESQ-C score	8	0.354	0.177		
$\dot{V}E$ ($l \cdot min^{-1}$)	8	9.8	2.6		
$P_{ET}CO_2$ (mmHg)	8	35.3	4.0		
$P_{ET}O_2$ (mmHg)	8	51.1	5.3		
SaO_2 (%)	8	82	4		
AMS+:					
ESQ-C score	12	1.974	1.093	0.795 to 2.447	0.001*
$\dot{V}E$ ($l \cdot min^{-1}$)	12	9.3	2.8	-2.1 to 3.1	0.692
$P_{ET}CO_2$ (mmHg)	12	35.9	4.0	-4.5 to 3.2	0.739
$P_{ET}O_2$ (mmHg)	12	50.8	6.7	-5.6 to 6.2	0.916
SaO_2 (%)	12	78	9	-2.6 to 11.9	0.197

*Mann-Whitney Rank Sum Test

Table 3. Resting ventilatory parameters at sea level segregated by AMS susceptibility.

Variable	n	Mean	±S.D.	95% C.I. of Difference	p
AMS-:					
$\dot{V}E$ ($l \cdot min^{-1}$)	8	9.8	2.2		
$P_{ET}CO_2$ (mmHg)	8	39.5	4.1		
$P_{ET}O_2$ (mmHg)	8	109.5	5.8		
SaO_2 (%)	8	97	1		
$\dot{V}E_{CHX}$ ($l \cdot min^{-1}$)	8	12.0	3.5		
SaO_{2CHX} (%)	8	88	2		
HVR ($\Delta\dot{V}E \cdot \Delta SpO_2^{-1}$)	8	0.44	0.20		
HVD ($l \cdot min^{-1}$)	8	0.93	0.85		
AMS+:					
$\dot{V}E$ ($l \cdot min^{-1}$)	12	9.2	2.3	-1.6 to 2.7	0.596
$P_{ET}CO_2$ (mmHg)	12	39.9	3.7	-4.1 to 3.3	0.815
$P_{ET}O_2$ (mmHg)	12	109.4	4.4	-4.6 to 4.9	0.948
SaO_2 (%)	12	97	1	-1 to 1	0.879*
$\dot{V}E_{CHX}$ ($l \cdot min^{-1}$)	12	9.8	2.9	-0.9 to 5.2	0.151
SaO_{2CHX} (%)	12	86	4	-2 to 5	0.348
HVR ($\Delta\dot{V}E \cdot \Delta SpO_2^{-1}$)	12	0.40	0.29	-0.20 to 0.30	0.699
HVD ($l \cdot min^{-1}$)	12	2.30	1.92	-0.17 to 2.89	0.025*

*Mann-Whitney Rank Sum Test

Figure 1. Sea level ventilatory protocol illustrating the time line and sequence of the normoxic (NOX), acute isocapnic hypoxic (AHX) and chronic isocapnic hypoxic (CHX) measurements.

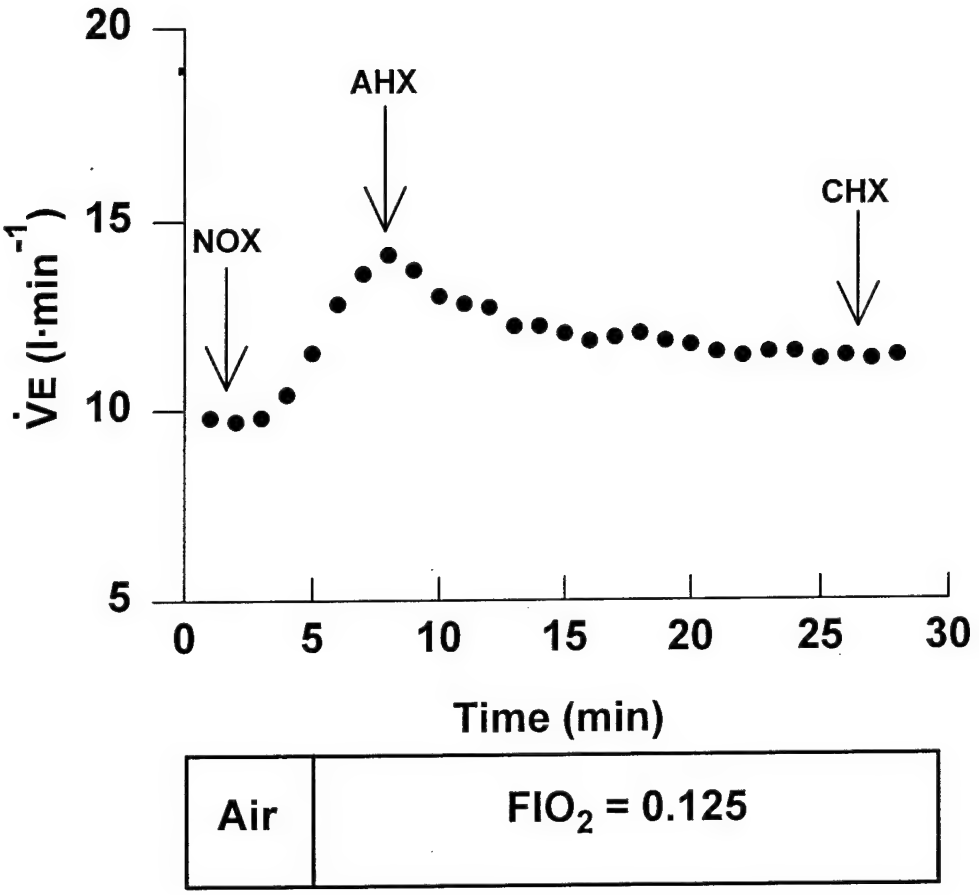
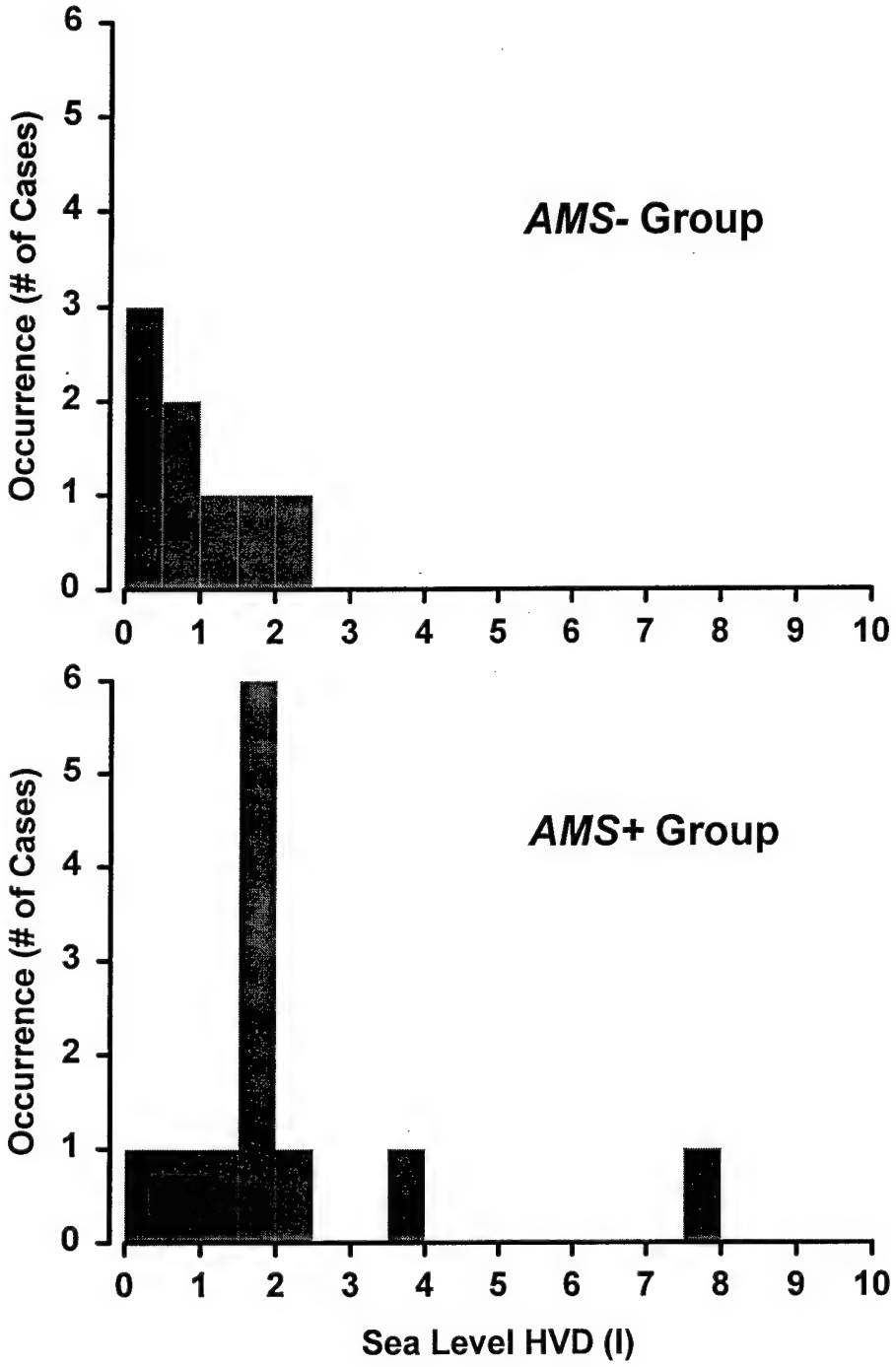


Figure 2. Histograms showing distribution of the sea level determined Hypoxic Ventilatory Depression (HVD) for AMS susceptible (AMS+) and non-susceptible (AMS-) subjects.



DISCUSSION

This study tested the hypothesis that individuals with lower effective ventilation at sea level (i.e., higher resting $P_{ET}CO_2$), and greater ventilatory depression in response to 30 minutes sustained isocapnic hypoxia would be at greater risk for developing AMS during exposure to high altitude. The basis for the hypothesis was the observation that AMS is more likely to develop in subjects with the lowest arterial oxygen saturation relative to well subjects at that same elevation. Our results do not support this hypothesis. We did find a significantly greater HVD in AMS susceptible subjects, but no other sea level ventilatory parameter distinguished between AMS-susceptible and non-susceptible subjects.

Our subjects demonstrated a wide range of interindividual differences in ventilation at sea level and high altitude and the differences at altitude were related to ventilatory differences among individuals before ascent. Normoxic resting $P_{ET}CO_2$ at sea level was related significantly to $P_{ET}CO_2$ at altitude. These results are in agreement with those reported by Reeves et al. (19) in men and by Muza et al. (17) in women. We expected these observations and hypothesized that subjects with lower effective ventilation at sea level and altitude would be more susceptible to developing AMS. But, at high altitude prior to development of AMS, we did not find significantly lower ventilation in the AMS-susceptible subjects relative to the well subjects. This latter observation is consistent with recently reported findings by Roach et al. (21). Thus, it was not surprising that the pre-ascent sea level resting $P_{ET}CO_2$ did not discern between the AMS-susceptible and non-susceptible subjects.

Previous studies (11,15,24,25) have observed HVD in humans during residence at high altitude. Moore et al. (15) reported that subjects with a prior history of moderate-to-severe AMS had not only a lower HVR to the acute hypoxia, but also a greater subsequent blunting of ventilation (i.e., HVD). However, their method of inducing sustained hypoxia at their baseline altitude (1,500 m) did not distinguish between the AMS-susceptible and non-susceptible subjects. Our approach to inducing sustained isocapnic hypoxia at sea level did produce a wide distribution of HVD in our subjects (Figure 2). Moreover, our AMS-susceptible subjects did demonstrate a significantly greater HVD than the non-susceptible subjects. However, the difference between the two groups was relatively small, and more importantly, there was large overlap between the AMS-susceptible and non-susceptible

subjects. Finally, in a subset of our subjects (n = 10) we were able to repeat the sea level HVD measurements (data not reported) about one month apart from the reported results. In this group HVD reproducibility was poor. Thus, we conclude that measurement of isocapnic HVD by the technique we used is not a practical approach to identifying AMS-susceptibility prior to ascent.

Our hypothesis that sea level measures of ventilation under normoxic and short-term isocapnic hypoxia can identify AMS-susceptible individuals was based on the observation that at high altitude hypoxemia is greater in those individuals developing AMS or sick with AMS (1,3,8,12,15,20,27). However, our study and several others have not always shown a clear distinction in the magnitude of hypoxemia between AMS-susceptible and non-susceptible subjects. Roach et al. (20) had suggested that resting SaO_2 at high altitude may be a good predictor of AMS-susceptibility because it represents the outcome of a number of factors including barometric pressure, ventilation, gas exchange and the oxygen-hemoglobin dissociation curve. Furthermore, measurement of SaO_2 is simple, reliable and easy to do in a field environment. In our study, the lowest SaO_2 measurements observed were in the AMS-susceptible subjects. But, only 4 out of 12 of our AMS-susceptible subjects had an SaO_2 at high altitude lower than any of the non-susceptible subjects. Recently, Roach et al (21) reported that in seven men exposed to 4,800 m in a hypobaric chamber, resting SaO_2 was not related to AMS. That study did find that AMS was exacerbated by prolonged submaximal exercise, possibly by exercise-induced hypoxemia. Measurement of awake, resting SaO_2 alone is probably not an accurate representation of the actual hypoxemia experienced by individuals at high altitude. Not only is hypoxemia exaggerated by exercise, but also during sleep (33). Thus, we suggest that a cumulative SaO_2 score incorporating SaO_2 measurements made on a regular schedule during rest, exercise and sleep may increase the specificity of SaO_2 as a predictor of AMS.

The lack of a strong correlation between ventilation and AMS susceptibility also probably reflects the multifaceted aspects of the illness. Fluid retention and antidiuresis has been associated with individual susceptibility to AMS and other altitude-induced illnesses (7,26,32). Hackett et al. (7) found a high correlation of both incidence and severity between the symptoms of AMS, HAPE, HACE and peripheral edema following rapid ascent to high altitude, and suggested that abnormalities in body fluid regulation

may be central to development of these edemas. Other investigators have also reported that the susceptibility to AMS is increased in those people that have reduced urine outputs during the first few days at altitude (13,26,32). Successful altitude acclimatization and absence of AMS, in contrast, is associated with diuresis and a rapid resolution of the symptoms of altitude illness (8,26). Another factor, which may determine susceptibility to AMS, is cranium or spinal column volumes. Recently we reported (16) that in AMS-susceptible and non-susceptible individuals, brain volume increased by about 2% during 32 h high altitude exposure. It has been suggested that AMS develops in those individuals who cannot accommodate the brain volume increase because of relatively small cranium and spinal column volume (23).

In summary, this study found that sea level pre-ascent measures of ventilation during normoxic or sustained isocapnic hypoxia were minimally effective in identifying AMS-susceptible verses non-susceptible subjects. Sea level normoxic resting $P_{ET}CO_2$ was related significantly to the magnitude of effective ventilation at altitude, and may be useful in identifying individuals in need of slower or staged ascent profiles to induce acclimatization. Finally, an effective means of identifying AMS-susceptible subjects may require a more robust multi organ system approach including ventilation, body fluid regulation and brain volume to cranium volume assessments.

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